ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR METHACRYLONITRILE

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Mechanism of Toxicity

Metabolic release of cyanide via cytochrome P450 hydroxylation through an epoxide intermediate

HISTORY OF METHACRYLONITRILE TSD

First discussed at the September, 1998, NAC meeting

Subsequently discussed by the COT subcommittee in March, 2001.

Suggestions made by the COT subcommittee have been incorporated into the revised TSD.

MAJOR CONCERN:

Proposed values were not consistent with the overall data set.

Modifications are as follows:

AEGL-1 values are now derived.

AEGL-2 values are based on chemical-specific data, not AEGL-3 divided by 3.

AEGL-3 is not based on mouse data, but is based on rat data because mouse data yielded values inconsistent with the human irritation data.

Time scaling is done with n= 1 or n= 3 (default), not the cyanide 'n' value of n= 2.6.

Summary of Proposed AEGL Values for Methacrylonitrile:MARCH, 2001						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Insufficient data to derive AEGL-1 values
AEGL-2	1.5 ppm	1.5 ppm	1.1 ppm	0.70 ppm	0.50 ppm	⅓ of the AEGL-3 values
AEGL-3	4.5 ppm	4.5 ppm	3.4 ppm	2.0 ppm	1.5 ppm	4-hr no-effect-level for death in mice (Pozzani et al., 1968)

AEGL-1 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
2 ppm	2 ppm	2 ppm	2 ppm	2 ppm

Species:	Human (7-9/group)
Concentration:	2 ppm
Time:	10 minutes
Endpoint:	Transient nasal, ocular, or throat irritation
Reference:	Pozzani et al., 1968

Time Scaling: Concentration held constant across all time points because mild irritant effects generally do not vary greatly over time.

Uncertainty Factors:

Interspecies = 1 Subjects were human

Intraspecies = 1 Considered sufficient because:

Similar transitory irritation was noted at 14 ppm, a concentration 7-fold higher than the point of departure for the AEGL-1 values.

AEGL-2 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
22 ppm	22 ppm	18 ppm	11 ppm	7.5 ppm

Species: Rat (22-23/pregnant/group)
Concentration: 100 ppm
Time: 6 hours/day, GD 6-20
Endpoint: 13-15% decreased fetal body weight; Maternal NOEL
Reference: Saillenfait et al., 1993

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute, 1-hour, and 4-hour time periods, and $n = 1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-2 was also adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 3 Considered sufficient because:

Use of the full uncertainty interspecies factor of 10, would yield AEGL-2 values that are not consistent with the total data set: 7.6 ppm for 10- and 30-minutes, 6.1 ppm for 1-hour, 3.8 ppm for 4-hours, and 2.5 ppm for 8-hours. However, humans exposed to 14 ppm methacrylonitrile for 10 minutes experienced only transient ocular, nasal, or throat irritation (Pozzani et al., 1968).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 10

AEGL-3 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
32 ppm	32 ppm	25 ppm	13 ppm	13 ppm

Species: Rat (6/sex/group)
Concentration: 176 ppm
Time: 3 hours
Endpoint: No mortality; loss of consciousness
Reference: Pozzani et al., 1968

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 4-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 was also adopted as the 10-minute value. The 4-hour value was adopted as the 8-hour value because extrapolation would yield an 8-hr AEGL-3 value less than the 8-hour AEGL-2 value.

Uncertainty Factors:

Interspecies = 3 Considered sufficient because:

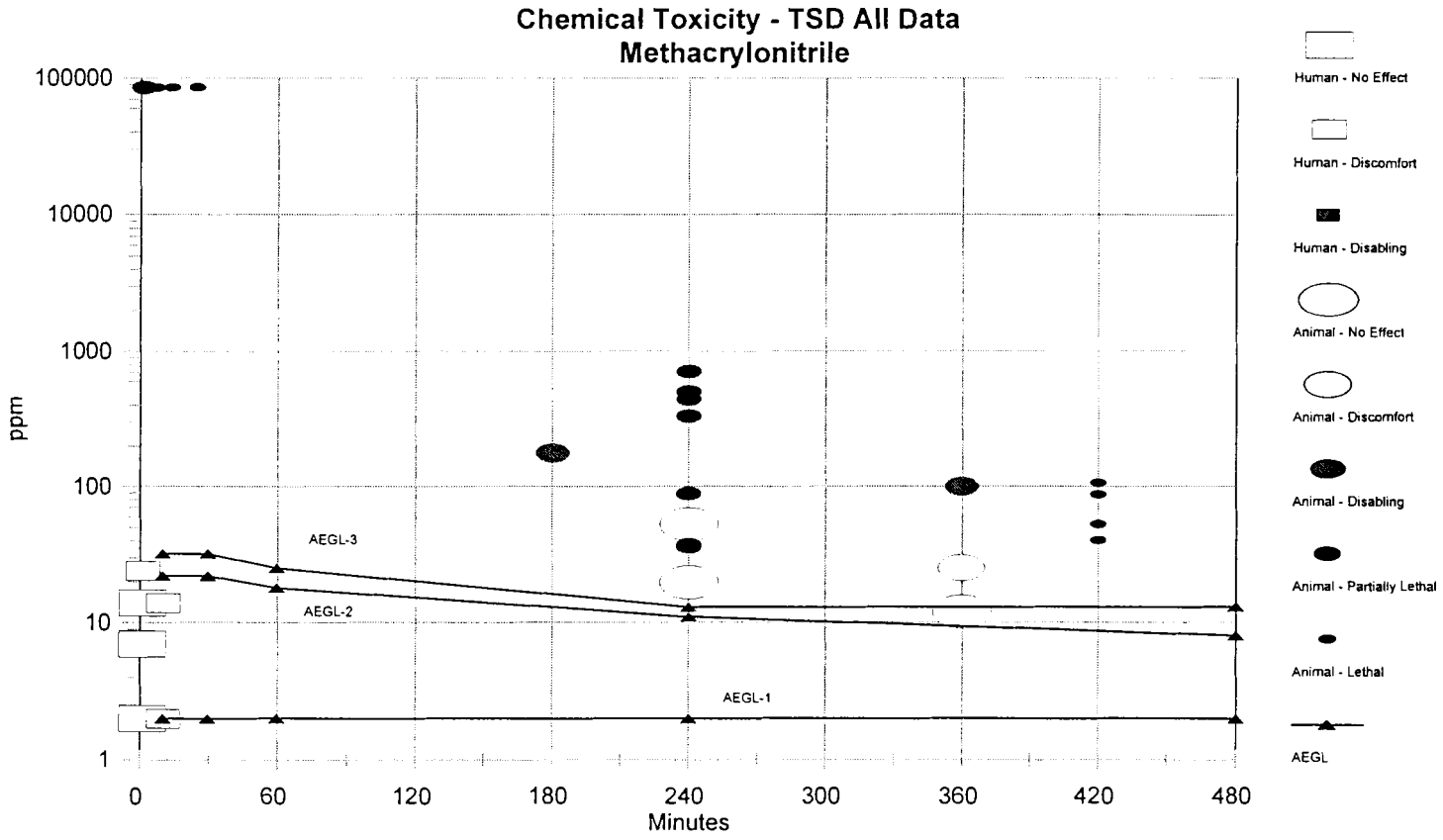
Use of the full uncertainty interspecies factor of 10, would yield AEGL-3 values that are not consistent with the total data set: 11 ppm for 10- and 30-minutes, 8.5 ppm for 1-hour, 4.4 ppm for 4-hours, and 2.2 ppm for 8-hours. However, humans exposed to 14 ppm methacrylonitrile for 10 minutes experienced only transient ocular, nasal, or throat irritation (Pozzani et al., 1968).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 10

EXTANT STANDARDS AND GUIDELINES FOR METHACRYLONITRILE					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	2.0 ppm	2.0 ppm	2.0 ppm	2.0 ppm	2.0 ppm
AEGL-2	22 ppm	22 ppm	18 ppm	11 ppm	7.5 ppm
AEGL-3	32 ppm	32 ppm	25 ppm	13 ppm	13 ppm
REL-TWA (NIOSH)	-	-	-	-	1 ppm
TLV-TWA (ACGIH)	-	-	-	-	1 ppm


Chemical Toxicity - TSD All Data
Methacrylonitrile
100000
10000
1000
100
10
1
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL